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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,782	10/17/2003	Harald W. Sontheimer	2006636-0064	7705

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,782	SONTHEIMER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15-20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15-20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-31-07 has been entered.

Applicants' amendment filed 10-31-07 has been entered. Claims 1 and 15 have been amended. Claims 21 and 26-28 have been canceled. Claims 1, 15-20 and 22-25 are pending and under consideration.

Claim Objections

2. Claim 20 is objected to because of the following informalities: There are two phrases of "selected from" in lines 1 and 2. Deleting one would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 16 recites the limitation "wherein the neuroectodermal tumor is a tumor type **treated**" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Claim 1 reads on delivering a cytotoxic moiety to a neuroectodermal tumor rather than treating a neuroectodermal tumor, and it is unclear what tumor type is "treated".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 15-20 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering chlorotoxin fused to a cytotoxic moiety to neuroectodermal tumors in vitro, does not reasonably provide enablement for delivering a cytotoxic moiety to a neuroectodermal tumor in vivo by administering a pharmaceutical composition comprising a chlorotoxin fused to a cytotoxic moiety to an individual via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 15-20 and 22-25 are directed to a method of delivering a cytotoxic moiety to a neuroectodermal tumor comprising administering a **pharmaceutical** composition comprising an agent consisting of chlorotoxin fused to a cytotoxic moiety to an individual having a neuroectodermal tumor, such that the agent specifically binds to the tumor. Claims 15 and 21 specify the cytotoxic moiety is selected from the group as recited in the claims. Claims 16 and 20 specify the tumor is selected from the group as recited in the claims. Claim 17 specifies the chlorotoxin can be native, synthetic, or recombinant chlorotoxin. Claims 18 and 19 specify the neuroectodermal tumor is a glioma. Claim 22 specifies the composition further comprises a pharmaceutically acceptable carrier. Claims 23 and 24 specify the composition is suitable for

parenteral administration, such as intravenous, intramuscular, intrathecal and subcutaneous administration. Claim 25 specifies the dose of chlorotoxin is effective to reduce the size of the tumor.

The specification only discloses the detection of glioblastoma, neuroblastoma, medulloblastoma, pheochromocytoma and metastatic melanoma etc. in a tissue sample by using chlorotoxin. The claims encompass delivering a cytotoxic moiety to various neuroectodermal tumors, including ependymonas, medulloblastomas, meuroblastomas, gliomas, gangliomas, pheochromocytomas, melanomas, small cell lung carcinoma, Ewing's sarcoma, and metastatic tumors in the brain, in vivo by administering a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety or cytotoxic moiety recited in claim 15 via various administration routes. The specification fails to provide adequate guidance and evidence for how to deliver various cytotoxic moieties to various neuroectodermal tumors in vivo via various administration routes, including intraperitoneal, oral, topical, intravenous, intramuscular, intrathecal and subcutaneous administration etc. The specification only discloses in vitro data of how to deliver the cytotoxic moiety to a tissue sample, however, such in vitro data fails to enable the in vivo administration of chlorotoxin-cytotoxic moiety to various neuroectodermal tumors in vivo.

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) shows several factors that contribute to the unpredictability of gene transfer in vivo. Those factors include the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the

trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced (e.g. bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198), reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy (e.g. abstract). Similarly, the administration route, the location of the target cells, the stability of the polypeptide, and the amount of the polypeptide that reaches the target site will determine the efficiency of protein transfer in vivo. The state of the art of gene or protein transfer (the cytotoxic moiety can be a nucleic acid or a protein) was unpredictable at the time of the invention. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids.

Further, several neuroectodermal tumors are located in the brain. It was well known in the art that brain is separated from general circulation by the blood brain barrier. Castro et al., 2001 (Histl. Histopathol., Vol. 16, p. 1225-1238) points out that the brain offers a particular challenge for gene delivery to its constituent cells because it is "made up of mostly non-dividing cells, the skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain" (e.g. abstract). "The main challenges holding back the widespread clinical implementation of neurological gene therapy are technical limitations of current transgene delivery system, i.e. the gene transfer vectors...short term

expression of the potentially therapeutic transgenes, coupled to the instability of vectors in the presence of the inflammatory and immune responses directed against the vectors and/or transgenes, reduce the efficiency of delivered therapeutic transgenes...Factors affecting vector stability in target cells/tissues, remain to be identified" (e.g. page 1226, right column). Similarly, there is the brain-barrier to the delivery of a protein, such as the chlorotoxin fused to a cytotoxic protein moiety as recited in the claims, to the brain. It is unclear how the chlorotoxin complex would reach the targeted tumor in the brain via oral administration, topical administration, intravenous administration, intramuscular administration, subcutaneous administration, or intrathecal administration etc., to a subject. The specification fails to provide adequate guidance and evidence for whether sufficient chlorotoxin fused to any cytotoxic moiety could reach target neuroectodermal tumor in a subject via various administration routes such that said delivery can be detected in vivo. Whether chlorotoxin-cytotoxic moiety would be able to reach various neuroectodermal tumors in a subject via various administration routes was unknown at the time of the invention and the specification fails to provide sufficient enabling data for the claimed delivery method. There is no evidence of record that shows the chlorotoxin-cytotoxic moiety can reach various neuroectodermal tumors in vivo via various administration routes such that said delivery can be detected in vivo.

Claim 25 specifies the dose of chlorotoxin is effective to reduce the size of the tumor. Chlorotoxin (CTX) is a small peptide purified from Leiurus quinquestriatus scorpion venom and CTX binds specifically to the glioma-specific chloride ion channel on glioma cells see abstract, Soroceanu et al., 1998, Cancer Research, Vol. 58, p. 4871-4879). It appears that chlorotoxin itself functions as a carrier of the cytotoxic moiety. The specification fails to provide adequate

guidance and evidence for what dose of the chlorotoxin would be able to reduce the size of various neuroectodermal tumors in vivo. There is no evidence of record that shows chlorotoxin itself would be able to reduce tumor size in vivo or in vivo. If there is any effect on reducing the size of a tumor in vivo, it would depends on the toxicity of the cytotoxic moiety fused to the chlorotoxin and such effect would vary among different cytotoxic moieties used and its administration route.

The term "**pharmaceutical**" in claim 1 implies therapeutic effect in vivo and claim 25 specifies that the dose of chlorotoxin is effective to reduce the size of the tumor. Therefore, claims 1, 15-20 and 22-25 read on gene therapy and protein therapy in vivo. The claims encompass treating various neuroectodermal tumors in vivo by administering a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety or cytotoxic moiety recited in claim 15, i.e. gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin, or any complement protein, to an individual via various administration routes so as to provide therapeutic effect for treating said neuroectodermal tumor in vivo. The specification fails to provide adequate guidance and evidence for how to treat a neuroectodermal tumor, such as ependymomas, medulloblastoma, pheochromocytoma, glioblastoma, neuroblastoma, or any metastatic tumors of neuroectodermal origin in the brain, by using a pharmaceutical composition comprising a chlorotoxin fused to a cytotoxic moiety, such as gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin, or any complement protein, via various administration routes in vivo.

The claims read on gene therapy and protein therapy in vivo. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101)

shows several factors that contribute to the unpredictability of gene transfer or gene therapy in vivo. Those factors include the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, which are all important factors for a successful gene therapy (e.g. bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198), reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy (e.g. abstract). Similarly, the administration route, the location of the target cells, the stability of the polypeptide, and the amount of the polypeptide that reaches the target site will determine the efficiency of protein transfer and whether said protein can provide therapeutic effect for a particular disease in vivo. The state of the art of protein therapy was also unpredictable at the time of the invention. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids, and as discussed below, there is blood-brain barrier for treating brain tumors. Whether sufficient chlorotoxin-cytotoxic protein moiety would reach target neuroectodermal tumor in a subject to provide therapeutic effect depends on the concentration of the chlorotoxin complex used, the administration route, the location of the target cells and the stability of the polypeptide etc.

In addition, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins. Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). The claims encompass various different cytotoxic moiety and the recited different toxins, antiviral protein, and complement proteins. Different proteins have different amino acid sequences and the biological function of a

protein was unpredictable from mere amino acid sequence at the time of the invention. The dose of the cytotoxic moiety, the stability of said cytotoxic moiety during protein transfer in vivo, and the effect of the cytotoxic moiety on treating neuroectodermal tumor all vary among different cytotoxic moieties., however, the specification fails to provide such specific guidance for those various cytotoxic moieties recited in the claim. Thus, one skilled in the art would not know how to treat numerous neuroectodermal tumors in vivo by using various chlorotoxin-cytotoxic moiety complexes via various administration routes so as to provide therapeutic effect for treating said neuroectodermal tumor.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, the level of skilled artisan which is high, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER